**SUPPLEMENTAL MATERIAL**

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## 1. Supplemental Methods

*Patient Recruitment and Angiography*

We recruited patients from the Vanderbilt University Medical Center (VUMC) cardiac catheterization laboratory from May 2003 – April 2005 and August 2021 – August 2022 under the VUMC Institutional Review Board approval #090828. Adult patients without existing hematologic malignancy undergoing a planned cardiac procedure were enrolled (**Supplemental Figure 1**). The referring provider recorded angiography indications. Records were excluded if coronary angiography data was not entered or if the indication was STEMI. Coronary angiography was performed using standard imaging techniques as directed by the operator. Coronary angiography interpretation was performed by the operator at the time of the procedure. Obstructive stenosis was defined as ≥50% stenosis in the left main coronary artery or ≥70% stenosis in all other coronary arteries.

*Next Generation Sequencing and CHIP ascertainment*

An EDTA anticoagulated blood sample was collected prior to the planned procedure and used for DNA isolation. DNA was extracted using Qiagen QIAamp DNA Mini Kit per manufacturer's instructions. Next generation sequencing was performed using a targeted oligonucleotide-based sequencing panel[26] (Twist Biosciences) to >500x depth on the Illumina sequencing platform (Illumina, California, USA). CHIP variant status was determined as previously described[27]. Briefly, somatic mutations were called from CRAM files using Mutect2 software which is optimized for somatic variant calling on the Terra cloud computing platform[28]. Variants were annotated using ANNOVAR and subsequently filtered against known CHIP variants[29] (**Supplemental Table 1**). Variants meeting filtration criteria and a minimum of three alternate reads and VAF of greater than 2% were retained, which aligns with the minimum VAF set forth by the WHO for CHIP diagnosis[30]. Somatic variant ascertainment was confirmed via Binomial test. The measured read depth for the variant was determined to be statistically different from

half of the sum of all sequencing reads at that site, as would be true for heterozygous germ line variants. We conducted a binomial test across all variants and flagged variants that failed the binomial test at $P < .01$ as is standard practice in the literature[1–3,27].

*Data Acquisition, Management, and Storage*

Angiography results, laboratories, and anthropometric data were extracted from the electronic health record and compiled in a Redcap database during a single extraction period in December 2022. Study personnel were blinded to CHIP status until the final analysis was performed. A modified version of the Gensini Score was used to estimate coronary artery disease severity[31] (**Supplemental Table 2**). To calculate the modified Gensini Score, vessel segments were scored from 0-32 according to lesion severity (0 for 0% stenosis, 1 for 1-25% stenosis, 2 for 25-50% stenosis, 4 for 50-75% stenosis, 8 for 75-90% stenosis, 16 for 90-99% stenosis, and 32 for 100% stenosis) and then multiplied by segment-specific multipliers, with greater weight given to lesions in more proximal vessels segments (e.g. multiplier of 5 for left main coronary artery lesions versus 2.5 for proximal left anterior descending artery lesions). The total modified Gensini score was calculated as the sum of all vessel segment scores. Scores were not adjusted for collateral blood flow or right-versus left-dominant circulation.

*Statistics*

Continuous data were compared using Mann-Whitney $U$ tests. Binned data were compared using $\chi^2$ tests with post-hoc two-by-two $\chi^2$ tests where applicable. Multivariable logistic regression models and proportional odds models were used to assess the association between CHIP status and binary (presence of stenosis) and ordinal (degree of stenosis, number of stenoses) variables, respectively, using the *Hmisc* and *rms* packages[20,21]. Given the non-normal distribution of the data, proportional odds models were chosen due to the heavily zero-skewed nature of data from the cardiac catheterization laboratory. For example, a plurality of patients

will have no left main artery stenosis noted, with a tail from 1-100%. The proportional odds assumption was tested, and no violations were identified. Odds ratios in these models were adjusted by age, age$^2$, sex, race, ethnicity, hyperlipidemia, statin use, hypertension, diabetes, and smoking status. All odds ratios are reported with 95% confidence intervals. Statistical $\alpha$ was set to 0.05 and the Holm-Šídák method was used for multiple hypothesis correction of P values[32]. Statistical analyses were performed using the statistical programming language, R, version 4.3.1.

## 2. Supplemental Tables

**Supplemental Table 1.** CHIP Panel Contents

| Gene | Chromosome | Base Pairs |
|------|-----------|------------|
| ASXL1 | 20 | 32358770-32358837; 32359741-32359796; 32366378-32366472; 32369006-32369128; 32428122-32428253; 32428319-32428427; 32429332-32429436; 32429895-32430058; 32431315-32431489; 32431577-32431684; 32432874-32432990; 32433278-32433922; 32434426-32437343 |
| ASXL2 | 2 | 25749689-25750420; 25753532-25753640 |
| BRCC3/MTCP1 | X | 155071527-155071650; 155072326-155072343; 155073376-155073431; 155077169-155077289; 155078615-155078703; 155089262-155089351; 155090783-155090839; 155099314-155099389; 155116056-155116188; 155116710-155116754 |
| CBL | 11 | 119278160-119278302; 119278504-119278718 |
| DNMT3A | 2 | 25234273-25234425; 25235701-25235830; 25236930-25237010; 25239124-25239220; 25239484-25239518; 25240296-25240455; 25240634-25240735; 25241556-25241712; 25243892-25243987; 25244149-25244343; 25244534-25244657; 25245247-25245337; 25246014-25246069; 25246154-25246314; 25246614-25246781; 25247045-25247163; 25247585-25247754; 25248031-25248257; 25249651-25249729; 25251906-25252099; 25252188-25252202; 25274935-25275092; 25275494-25275548; 25282382-25282716; 25300133-25300248; 25313907-25313989 |
| ETNK1 | 12 | 22671265-22671359 |
| GNAS | 20 | 58909344-58909428; 58909515-58909584; 58909678-58909809; 58909945-58910086; 58910328-58910406; 58910677-58910834 |
| GNB1 | 1 | 1806469-1806543; 1815750-1815867 |

| Gene | Chr | Position |
|---|---|---|
| IDH1 | 2 | 208243524-208243601; 208248358-208248421 |
| IDH2 | 15 | 90088655-90088758 |
| JAK2 | 9 | 5073683-5073800 |
| KIT | 4 | 54727415-54727542; 54727822-54727927; 54728010-54728121; 54729334-54729485; 54731327-54731419; 54731870-54731998; 54736497-54736609 |
| KRAS | 12 | 25225612-25225772; 25227220-25227424; 25245270-25245384 |
| MPL | 1 | 43349257-43349363 |
| NRAS | 1 | 114713799-114713978; 114716047-114716162 |
| PPM1D | 17 | 60662989-60663557 |
| SETBP1 | 18 | 44951903-44952002 |
| SF3B1 | 2 | 197400049-197400171; 197400246-197400439; 197400709-197400941; 197401394-197401530; 197401736-197401893; 197401979-197402135; 197402550-197402831; 197402943-197403040; 197403579-197403769; 197405070-197405182; 197405269-197405477; 197407992-197408124; 197408363-197408586; 197409764-197410012; 197416735-197416916 |
| SRSF2/MFSD11 | 17 | 76736785-76736983 |
| TET2 | 4 | 105233891-105237445; 105241333-105241438; 105242828-105242932; 105243564-105243783; 105259613-105259774; 105261753-105261853; 105269604-105269752; 105272558-105272923; 105275042-105276524 |
| TP53 | 17 | 7669603-7669695; 7670603-7670720; 7673213-7673271; 7673301-7673344; 7673529-7673613; 7673695-7673842; 7674175-7674295; 7674814-7674976; 7675047-7675243; 7675988-7676277; 7676376-7676408; 7676515-7676627 |
| U2AF1 | 21 | 43093096-43093254; 43094461-43094568; 43094649-43094793; 43095432-43095541; 43095688-43095748; 43100447-43100524; 43101274-43101437; 43104309-43104407; 43107445-43107499 |
| ZBTB33 | X | 120253410-120255439 |

| ZNF318 | 6 | 43340784-43340913; 43342106-43342216; 43342670-43342884; 43348318-43348630; 43352371-43352481; 43354658-43356150; 43357120-43357770; 43365286-43365445; 43368961-43369370 |

**Supplemental Table 2.** Modified Gensini Score Calculation

| Vessel segments | Multiplier | Stenosis | Score |
|---|---|---|---|
| pRCA | 1 | 1-25% | 1 |
| mRCA | 1 | 26-50% | 2 |
| dRCA | 1 | 51-75% | 4 |
| PDA | 1 | 76-90% | 8 |
| PLB | 0.5 | 91-99% | 16 |
| LM | 5 | 100% | 32 |
| pLAD | 2.5 | | |
| mLAD | 1.5 | | |
| dLAD | 1 | | |
| LADD1 | 1 | | |
| LADD2 | 0.5 | | |
| pLCx | 2.5 | | |
| mLCx | 1 | | |
| dLCx | 1 | | |
| OM | 1 | | |
| OM2 | 1 | | |
| OM3 | 0.5 | | |
| RI | 1 | | |

**Supplemental Table 3.** Medication Use by CHIP Status

| | No CHIP | CHIP | P value |
|---|---|---|---|
| **Aspirin** | 63.4% (591) | 61.9% (130) | 0.68 |
| **P2Y12 Inhibitor** | 21.6% (202) | 26.1% (55) | 0.16 |
| **Anti-Coagulation** | 7.1% (67) | 7.1% (15) | 0.98 |
| *Dual Anti-Platelet Therapy* | 7.8% (73) | 12.3% (26) | 0.034 |
| *Double Therapy* | 3.2% (30) | 3.8% (8) | 0.67 |
| *Triple Therapy* | 0.2% (2) | 0.9% (2) | 0.1 |
| **Statin** | 59.7% (557) | 61.9% (130) | 0.57 |
| **Beta Blocker** | 47.7% (445) | 56.1% (118) | 0.027 |
| **ACE Inhibitor** | 28.2% (263) | 30.9% (65) | 0.43 |
| **ARB** | 19.4% (181) | 20.4% (43) | 0.73 |
| **CCB** | 27.5% (257) | 37.6% (79) | 0.0039 |
| **NO** | 23.4% (219) | 27.6% (58) | 0.21 |
| **Diuretic** | 42.9% (400) | 47.6% (100) | 0.21 |

**Supplemental Table 4.** Unadjusted Mann-Whitney *U* Tests for Stenosis Counts

| | N | # of Stenoses | | # of Obstructive Stenoses | |
|---|---|---|---|---|---|
| | | Median [IQR] | P Value | Median [IQR] | P Value |
| **No CHIP** | 932 | 2 [0, 4] | - | 0 [0, 2] | - |
| **DNMT3A** | 56 | 3 [0, 5] | 0.094 | 0 [0, 2.25] | 0.30 |
| **TET2** | 42 | 2.5 [1, 4.75] | 0.042 | 1 [0, 3] | 0.0026 |
| **Other** | 62 | 3 [0, 5.75] | 0.040 | 0.5 [0, 3] | 0.049 |
| **Multiple** | 50 | 3 [0, 5] | 0.022 | 1 [0, 2] | 0.054 |
| **VAF ≤ 10%** | 155 | 3 [0, 5] | 0.00025 | 1 [0, 3] | 0.0011 |
| **VAF > 10%** | 55 | 2 [1, 4] | 0.17 | 1 [0, 2.5] | 0.067 |